Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Table 15e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Hepatitis	Most ARV drugs have been associated with hepatitis, but there is a strong association between hepatitis and the use of NVP and EFV. NVP, EFV, ABC, RAL, DTG, and MVC have been associated with hepatitis in the context of HSRs. NRTIs, especially ZDV, have been associated with lactic acidosis and hepatic steatosis.	**Onset:** • Acute toxic hepatitis most commonly occurs within the first few months of therapy, but it can occur later. • Steatosis presents after months or years of therapy. • Patients with HBV coinfection may experience a hepatitis flare with the initiation or withdrawal of 3TC, FTC, TDF, or TAF. Flare may also occur with the emergence of resistance to 3TC or FTC (especially if the patient is receiving only one anti-HBV agent). Note that TDF and TAF have high barriers to resistance when used to treat HBV. • Hepatitis may be a manifestation of IRIS if it occurs early in therapy, especially in patients with HBV or HCV coinfection. **Presentation:** • Asymptomatic elevation of AST and ALT levels • Symptomatic hepatitis with nausea, fatigue, and jaundice • Hepatitis may present in the context of HSR with rash, lactic acidosis, and hepatic steatosis.	Uncommon	HBV or HCV coinfection Underlying liver disease Use of other hepatotoxic medications and supplements (e.g., St. John's wort [*Hypericum perforatum*], chaparral [*Larrea tridentata*], germander [*Teucrium chamaedrys*]) Alcohol use Pregnancy Obesity Higher drug concentrations of PIs **For NVP-Associated Hepatic Events in Adults:** • Female sex with pre-NVP CD4 count >250 cells/mm^3 • Male sex with pre-NVP CD4 count >400 cells/mm^3 • Population- specific HLA types[a]	**Prevention:** • Avoid concomitant use of hepatotoxic medications. • In patients with elevated levels of hepatic enzymes (>5 times to 10 times ULN) or chronic liver disease, most clinicians would avoid NVP. **Monitoring** *For ARV Drugs Other Than NVP:* • Obtain AST and ALT levels at baseline and at least every 3–4 months thereafter;[b] monitor at-risk patients more frequently (e.g., those with HBV or HCV coinfection or elevated baseline AST and ALT levels). *For NVP:* • Obtain AST and ALT levels at baseline, at 2 weeks, 4 weeks, and then every 3 months.	Evaluate the patient for other infectious and non-infectious causes of hepatitis and monitor the patient closely. **Asymptomatic Hepatitis:** • Potentially offending ARV drugs should be discontinued if ALT or AST level is >5 times ULN. **Symptomatic Hepatitis:** • Discontinue all ARV drugs and other potentially hepatotoxic drugs. • If a patient experiences hepatitis that is attributed to NVP, NVP **should be permanently discontinued**. • Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.

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Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Indirect Hyperbilirubinemia	ATV	**Onset:** • Within the first months of therapy **Presentation:** • May be asymptomatic or associated with jaundice • Levels of direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high. • Normal AST and ALT	In long-term follow-up, 9% of children who were receiving ATV had at least one total bilirubin level >5 times ULN and 1.4% of children experienced jaundice.	None established.	**Monitoring:** • No ongoing monitoring needed. • After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; levels may improve over time.	Isolated indirect hyperbilirubinemia is not an indication to stop ATV. Psychological impact of jaundice should be evaluated, and alternative agents should be considered. Jaundice may result in nonadherence, particularly in adolescents; this side effect should be discussed with patients.
Non-Cirrhotic Portal Hypertension	d4T, ddI The Panel **no longer recommends** the use of these agents.	**Onset:** • Generally after years of therapy; may occur years after stopping therapy. **Presentation:** • GI bleeding, esophageal varices, and hypersplenism • Mild elevations in AST and ALT levels, moderate increases in ALP levels, and pancytopenia **Liver Biopsy Findings:** • The most commonly seen findings include nodular regenerative hyperplasia and hepatoportal sclerosis.	Rare	Prolonged exposure to ddI and the combination of d4T and ddI.	No specific monitoring	Manage complications of GI bleeding and esophageal varices.

[a] For example, HLA-DRB1*0101 in white people, HLA-DRB1*0102 in South Africans, and HLA-B35 in Thai people and white people.

[b] Less-frequent monitoring can be considered in children whose clinical status has been stable for >2 years to 3 years (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).

Key: 3TC = lamivudine; ABC = abacavir; ALP = alkaline phosphatase; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; EBV = Epstein-Barr virus; EFV = efavirenz; FTC = emtricitabine; GI = gastrointestinal; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; the Panel = Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PI = protease inhibitor; RAL = raltegravir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal; ZDV = zidovudine

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